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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,538	10/23/2003	Michele Sanicola-Nadel	BINA117CN	4018

959 7590 11/01/2006

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,538	SANICOLA-NADEL ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-48,50,59,60 and 62-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *46-48,62,67 and 70-80* is/are allowed.

6)☒ Claim(s) *43-45,50,59,60,63-66,68 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/06;2/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 08/16/2006, and a response to the arguments is set forth.

2. Claims 1-42, 49, 51-58 and 61 have been cancelled

3. Claims 43, 45-48, 67 and 78 have been amended.

4. Claims 79 and 80 have been newly added.

5. Claims 43-48, 50, 59, 60 and 62-80 are under examination.

6. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

7. Please note that the search for the elected species, breast cancer, did not result in any prior art. Hence, the search is expanded to colon and pancreatic cancers; as such the species restriction between breast, colon and pancreatic cancers is withdrawn. However, the species election for the other components of the claim: testicular, lung, ovary, bladder, uterine, cervical and stomach is still valid.

Claim Objections

8. The objection of claims 46-48, 62, 70, 72 and 73-78 for reciting non-elected inventions is withdrawn.

The species election as set forth in the office action mailed on 03/16/2006 between SEQ ID NO:1 and SEQ ID NO:2, and the various antibodies (page 4 paragraph 3 of the office action mailed on 10/18/2005) is withdrawn.

Objections Maintained

9. The objection of claim 50 for reciting non-elected inventions is maintained. The species election for claim 50, between all different types of cancers, is maintained for testicular, lung, ovary, bladder, uterine, cervical and stomach, and hence the objection is maintained.

Rejections Withdrawn

10. The rejection of claim 43 as being vague and indefinite for reciting "a method of modulating growth of tumor cells", because the exact meaning of the word modulate is not clear is withdrawn in view of amendments to the claims.

The claims have been amended to recite "a method of inhibiting proliferation of tumor cells in a subject....", thus overcoming the rejection.

11. The rejection of claims 46, 47, 62, 70, 74 and 78 as being vague and indefinite for reciting "epitope of Cripto comprised in the domain spanning amino acid residues" because the exact meaning of the word scanning is not clear is withdrawn in view of applicants arguments.

The applicants have clearly defined scope of the claims (please see page 8 of the response filed on 08/16/2006).

12. The rejection of claim 67 is vague and indefinite for reciting "with a nonconjugated chemotherapeutic", because it is not clear as to what a nonconjugated chemotherapeutic is, is withdrawn in view of applicants arguments.

The applicants argue that it would be clear to one of ordinary skill in the art that a nonconjugated chemotherapeutic is intended to mean a chemotherapeutic agent that is not conjugated to the antibodies of the invention. The applicants have described various nonconjugated chemotherapeutic agents that are well known in the art.

13. The rejection of claim 76 is vague and indefinite for reciting "antibody specifically binds to a Cripto amino acid which inhibits the interaction of Cripto and ALK4", is withdrawn in view of applicants arguments.

The applicants argue that the specification teaches assays, at least in Example 8, at page 38, lines 1-22 that can be used to assess whether Cripto-specific antibodies inhibit Cripto's ability to bind to Alk4. Such binding assays were routine in the art at the time of the invention. These arguments are found persuasive and hence the rejection is withdrawn.

14. The rejection of claims 48, 71, 72, 77 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1)

known and readily available to the public; (2) reproducible from the written description is withdrawn.

The applicants has provided all the information to satisfy the Deposit Requirement (pages 10-11 bridging paragraph of response filed on 08/16/2006, in particular), hence the instant rejection is withdrawn.

15. The rejection of claim 78 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants amendments to the claims.

16. The rejection of claims 43, 44-47, 50, 58-60, 62-70, 74, 76, 78 under 35 U.S.C. 103(a) as being unpatentable over Qi et al (Journal of cancer. 1994, 69:903-910) in view of Meissner and Coleman (U.S. Patent 5981215, Date Issued: November 9, 1999) in view of Williams et al (PGPUB 20030232755, filed March 17, 2003 but claimed priority to September 18, 2000) in view of Dan et al (U.S. Patent 6,207,153, Filed 03/27/97) and further in view of Chari et al (U.S. Patent 6333410, Date filed: August 18, 2000) is withdrawn.

Williams et al (PGPUB 20030232755) and the instant application were, at the time the invention was made, owned by the same assignee. Hence the reference does not apply as prior art and the rejection is withdrawn.

17. The rejection of claims 43-48, 50, 58-60 and 62-78 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88-104 of copending Application No. 10/945,853 is maintained.

The applicants state that upon an indication of allowable subject matter in either of these application, Applicants will consider filing a terminal disclaimer.

The above statement is carefully considered, but not found persuasive to overcome the rejection. Hence, the rejection is maintained until the applicants either amend the claims or submit a terminal disclaimer.

New Grounds of Rejections

18. Claims 43-45, 50, 59, and 63-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Meissner and Coleman (U.S. Patent 5981215, Date Issued: November 9, 1999).

The instant claims are drawn to a method of inhibiting tumor cells in a subject comprising the step of administering to the subject an effective amount of a monoclonal antibody that binds Cripto and a pharmaceutically acceptable carrier, wherein the subject is human. In addition, the claims are drawn to a method of treating a subject having a tumor that over-expresses Cripto comprising administering to the subject a composition comprising a monoclonal antibody that binds to Cripto and a pharmaceutically acceptable carrier in an effective amount. The claims are further drawn to the method of claim 43, wherein the tumor cell is selected from the group

consisting of breast, colon and pancreatic tumor cells, wherein the antibody is humanized, wherein the antibody is an antibody fragment selected from Fab, F(ab') and a F(ab')2 fragment, is a full length, a single chain antibody.

Meissner and Coleman teach (abstract in particular) human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application; please see the attached sequence search). Meissner and Coleman teach that the cripto growth factor is one of the useful tumor markers known and that it is often upregulated in colon cancers and is expressed in pancreatic cancers (brief summary paragraph 5, in particular). Meissner and Coleman also teach antagonist against such polypeptides, wherein the potential CGF antagonist compounds includes antibodies, and their use as a therapeutic to treat and/or prevent neoplasia such as tumors, and, thereby competitively inhibiting the action of CGF (paragraph 70, in particular), wherein the antibody may be employed to inhibit tumor growth, directly or indirectly (paragraph 72). Meissner and Coleman teach that CGF is over expressed and secreted by certain types of cancer cell, for example, pancreatic cancers and colon cancers (paragraph 5 brief summary, in particular), and therefore detection of CGF gene transcription or an excessive amount of CGF protein allows cancer diagnosis. Accordingly, an anti-CGF antibody could be used to diagnose neovascularization associated with tumor formation since an altered level of Cripto polypeptide may be indicative of such disorders (paragraph 57). Meissner and Coleman further teaches that these antibodies can be, for example, polyclonal or monoclonal antibodies including

chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library (paragraph 94, in particular). In addition Meissner and Coleman teach that antibodies to CGF may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the antibody and a pharmaceutically acceptable carrier or excipient; and such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof such that the formulation should suit the mode of administration. (paragraph 75, in particular). Meissner and Coleman also teach that the pharmaceutical compositions may be administered in a convenient manner such as by the oral, topical, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes, in an amount which is effective for treating and/or prophylaxis of the specific indication (paragraph 77, in particular), in addition to suggesting that anti-Cripto antibodies can be used for human administration (paragraph 76, in particular).

Thus, Meissner and Coleman teach a method of inhibiting tumor growth by administering antibodies to CGF, wherein the tumor can be selected form pancreatic or colon in addition to teaching a pharmaceutical composition comprising anti-Cripto antibodies that may be administered in humans in an effective amount. Further, Meissner and Coleman teach that the antibodies can be monoclonal antibodies including chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library.

Hence, Meissner and Coleman anticipate the instant claims.

Response to arguments – The applicant states (pages 14-15 bridging paragraph of the response filed on 08/16/2006, in particular) "Meissner and Coleman disclose the use of antagonists against human Criptin Growth Factor polypeptide (CGF) ..... the reference does not teach or suggest methods of inhibiting tumor cell proliferation or treating a subject using antagonists of Cripto, let alone monoclonal antibodies to Cripto as required by the presently pending claims".

In response to the above arguments, the applicant is reminded that the instant claims are directed to a method of inhibiting tumor cell in a subject comprising administering to the subject an effective amount of a composition comprising a monoclonal antibody that binds to Cripto and a pharmaceutically acceptable carrier; all of which are taught by Meissner and Coleman (please see the description above).

Since the instant claims are not drawn to any particular sequence of Cripto, it is irrelevant what CGF polypeptide Meissner and Coleman performed their experiments with. Meissner and Coleman teach that the Cripto antibodies can be employed in inhibition of tumor growth (which indicates that the proliferation of tumor cells can be inhibited), that the antibody can be monoclonal and a composition with a pharmaceutically acceptable carrier, in addition to suggesting that anti-Cripto antibodies can be used for human administration.

New Grounds of Rejections and Response to Arguments

19. Claims 43-45, 50, 59, 60, 63-66, 68 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner and Coleman (U.S. Patent 5981215, Date Issued: November 9, 1999) in view of Queen et al (U.S. Patent 5530101; Date Issued: June 25, 1996) in view of Dan et al (U.S. Patent 6,207,153, Filed 03/27/97) and further in view of Chari et al (U.S. Patent 6333410, Date filed: August 18, 2000).

Claims 43-45, 50, 59, and 63-65 have been described supra. Claim 60 is drawn to the method of inhibiting proliferation comprising administration of said antibody wherein the antibody is human antibody; claim 66 is drawn to said method, wherein the antibody is conjugated to a chemotherapeutic agent, wherein the therapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin (claim 68), and further wherein the agent is maytansinoid.

Meissner and Coleman has been described supra. Meissner and Coleman does not teach the human antibody, and the conjugation of antibody to a chemotherapeutic agent, wherein the therapeutic agent is selected from the group consisting of a tumor-activated prodrug, a radionuclide and a toxin, and further wherein the agent is maytansinoid. These deficiencies are made up for by Queen et al, Dan et al and Chari et al.

Queen et al teach human and humanized antibodies (abstract, in particular). Queen et al further teach antibody conjugation to a variety of cytotoxic agents including

radioisotopes, chemotherapeutic drugs, toxins and the antibodies may be labeled or unlabeled for diagnostic purposes (see column 20, lines 1-33). In addition, Queen et al teach the pharmaceutical compositions comprising such antibodies.

Dan et al teach a monoclonal antibody H11 and antigen binding fragments that specifically bind to the antigen recognized by H11, the C-antigen, which is found specifically on neoplastic cells and not on normal cells (abstract in particular), wherein the antigen binding polypeptide fragment is selected from the group consisting of whole antibodies, antibodies, chimeric antibodies, Fab, F(ab), F(ab')2, full length, single chain V region fragments (scFv) including the conjugation of the antibodies to a chemically functional moiety such as modifiers, toxins, detectable labels, paramagnetic labels, and drugs (claim 15 and 16, in particular); and the therapeutic advantages of such single chain or fragment antibodies that are conjugated, including to a chemotherapeutic agent (brief description of the invention, in particular).

Chari et al (U.S. Patent 6333410, Date filed: August 18, 2000). Chari et al teach antibody drug-conjugates utilizing Maytansinoids as a conjugate (see brief summary of the invention, in particular) and the evaluation of such antibodies in humans.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the claimed method.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the antibodies to cripto-1 for

therapeutic advantages, based on the teachings of Meissner and Coleman because Meissner and Coleman teach (abstract in particular) human Criptin Growth Factor polypeptide (CGF) (SEQ ID NO:7, that is 100% identical to SEQ ID NO:1 of the instant application; please see the attached sequence search), in addition to teaching antibodies against such polypeptides, and their use as a therapeutic to treat and/or prevent neoplasia such as tumors, and, thereby competitively inhibiting the action of CGF, wherein the antibody may be employed to inhibit tumor growth, directly or indirectly.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method, specifically for colon and pancreatic cancers, because Meissner and Coleman teach that CGF is over expressed and secreted by certain types of cancer cell, for example, pancreatic cancers and colon cancers, and therefore detection of CGF gene transcription or an excessive amount of CGF protein allows cancer diagnosis. Accordingly, an anti-CGF antibody could be used to diagnose neovascularization associated with tumor formation since an altered level of Cripto polypeptide may be indicative of such disorders (paragraph 57). Meissner and Coleman further teaches that the antibodies to CGF which can be, for example, polyclonal or monoclonal antibodies including chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library; may be employed in combination with a suitable pharmaceutical carrier. Meissner and Coleman also teach that such compositions comprise a therapeutically effective amount of the antibody and a

pharmaceutically acceptable carrier or excipient which may be administered in an amount which is effective for treating and/or prophylaxis of the specific indication in addition to suggesting that anti-Cripto antibodies can be used for human administration.

Further, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the claimed method by combining the teachings of Meissner and Coleman with Queen et al, Dan et al and Chari et al because Queen et al teach human and humanized antibodies in addition to pharmaceutical compositins comprising such antibodies and because Dan et al teach that an antigen binding polypeptide fragment, an antibody, that can be used in therapeutic purposes wherein the antigen binding polypeptide fragment is selected from the group consisting of monoclonal antibodies, whole antibodies, chimeric antibodies, Fab, F(ab), F(ab')2, full length, single chain V region fragments (scFv) including the conjugation of the antibodies to a chemically functional moiety such as modifiers, toxins, detectable labels, paramagnetic labels, and drugs and the therapeutic advantages of such single chain or fragment antibodies that are conjugated, including to a chemotherapeutic agent, and because Chari et al teach antibody drug-conjugates utilizing Maytansinoids as a conjugate and the evaluation of such antibodies in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

20. Claims 46-48, 62, 67 and 70-80 are found allowable.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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Ph: (571) 272-8789

SHEELA HUFF
PRIMARY EXAMINER